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STEREOSPECIFICITY OF 1,3-DIPOLAR CYCLOADDITIONS OF CYCLIC NITRONES TO (E) and (Z)-β-NITROSTYRENES.

Marina Burdisso, Anna Gamba, Remo Gandolfi*, and Paolo Pevarello

Dipartimento di Chimica Organica, Università di Pavia,
V.le Taramelli 10, 27100 Pavia, Italy

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Abstract - 3,4-Dihydroisoquinoline-N-oxide (**1**) reacted readily with (E)-β-nitrostyrene in a regiospecific reaction to give a mixture of 4-nitro-5-phenylisoxazolidines **3a** and **4a** resulting from endo and exo (with respect to the nitro group) transition states, respectively. This cycloaddition was found reversible under mild conditions. A careful study disclosed ≥ 99.89% stereoselectivity thus narrowly circumscribing the possibility of stereochemical leakage over the cycloaddition and cycloreversion processes. Moreover, our experimental data showed that eventual loss of stereochemistry should be ascribed to base catalyzed isomerizations in the adducts and/or in the educts.
The reaction of **1** with (Z)-β-nitrostyrene (exo specific and regiospecific) turned out to be faster than that of the (E)-isomer. This is the first example of higher reactivity of a cis than a trans-alkene in 1,3-dipolar cycloadditions.
The endo-trans adduct **3a** cycloreverted faster than the exo-trans isomer **4a** which in turn underwent fragmentation more readily than the exo-cis **6a**. The cycloreversion rate was slightly enhanced by increased solvent polarity.
This study was extended to the reaction of 5,5-dimethylpyrroline-N-oxide with both the cited dipolarophiles.

INTRODUCTION

The mechanism of 1,3-dipolar cycloadditions[1] has been the subject of great controversy between Huisgen and Firestone over the seventies. The Huisgen's mechanism [(a) Scheme 1] entails a concerted but not synchronous approach of the reactants to give a transition state which bears partial charges and occurs early along the reaction coordinate.[2] By contrast Firestone has proposed a two step process [(b)] via a cyclo or extended spin paired diradical. The cyclo intermediate ring closes to cycloadducts while the extended one either cycloreverts to reactants or (in the case of allenyl-propargyl 1,3-dipoles with monosubstituted acetylenes) gives rise to the formation of 1,3-addition products.[3]

The stereospecificity of 1,3-dipolar cycloadditions supports the concertedness of the reaction and militates against stepwise (diradical or zwitterionic) processes. In fact it is very difficult to accept that diradicals of the type shown in Scheme 1 always isomerize considerably more slowly by rotation around the dipolarophile single bond than they revert to reactants or collapse to products. So it is not surprising that the Huisgen mechanism is, by far, more popular than the Firestone

one between experimentalists.

The question of concertedness in 1,3-dipolar cycloadditions has also been of oustanding interest among theoreticians over the last fifteen years. The results of different molecular orbital calculations have provided support for both the one step (ab initio calculations at the molecular orbital level[4-6] and EH calculations[6]) and the stepwise (ab initio calculations with inclusion of extensive electron correlation[7], MINDO/2[6], MINDO/3[8] and MNDO[9a] semiempirical methods) mechanism. To account for the stereospecificity of the reaction in the framework of the two step process (MINDO/3 calculations) Lluch and Bertran have claimed that "the primitively double bond of the ethylenic dipolarophile maintains a high double bond character not only in the intermediate but even in the second transition state"[8] which leads to the final product.

Very recently Dewar[9b] has attempted to reconcile Huisgen's and Firestone's proposals on the basis of a third mechanistic alternative, i.e."a concerted but non synchronous mechanism, involving biradical-like or zwitterionic intermediates formed without specific activation from the 1,3-dipole and dipolarophile, where the second stage is rate determining". This mechanism "explains the stereospecificity of these reactions without the need to make ad hoc assumptions".

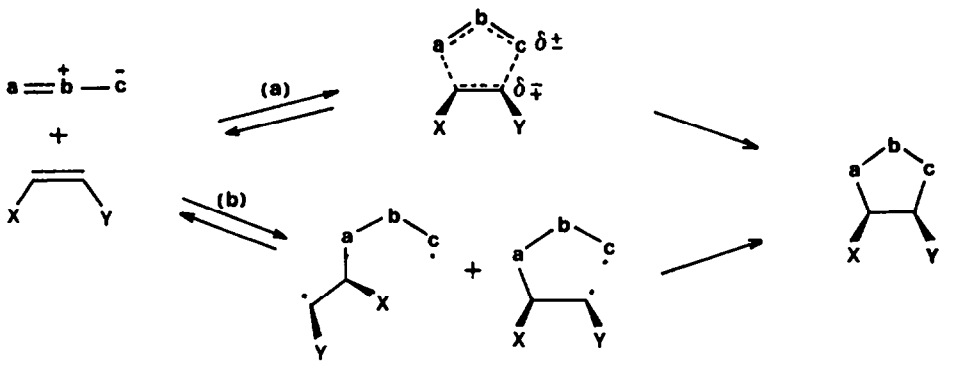
This brief summary of achievements of theoreticians[10] shows that, for the time being, there is still room for experimental research on concertedness of 1,3-dipolar cycloadditions as clearly shown by the elegant study by Huisgen et al. who established a>99.997% stereoselectivity for the reaction of diazomethane with methyl tiglate.[11a] Moreover in spite of the "well known stereospecificity" of 1,3-dipolar cycloadditions the borderline between concerted and non concerted processes has not yet been fully explored[12,13], and >99% stereoselective reactions are not commonly known for 1,3-dipolar cycloadditions due to the fact that the detection limits of the missing isomer has almost never been specified. In particular it should be worth exploring the borderline between concerted mechanisms and mechanisms via intermediates with prevailing zwitterionic character. In fact Huisgen et al. have very recently reported the first example of a two-step non-stereospecific 1,3-dipolar cycloaddition via a zwitterion.[11b] This reaction involves persubstituted (at one of the terminal atoms) electron-rich thiocarbonyl ylides and electron-poor dipolarophiles such as dimethyl 2,3-dicyanofumarate.[11b]

The lively interest in this topic[1,11b,14] and the appearance of two recent papers[13,15] dealing with the stereoselectivity of the cycloadditions of azomethine imines with (E) and (Z)-β-nitrostyrene prompt us to communicate the results found in the related reactions of the same dipolarophiles with cyclic nitrones.[16] These reactions also disclosed interesting aspects concerning endo-exo selectivity, cycloreversion processes and relative reactivity of (E) and (Z) isomers.

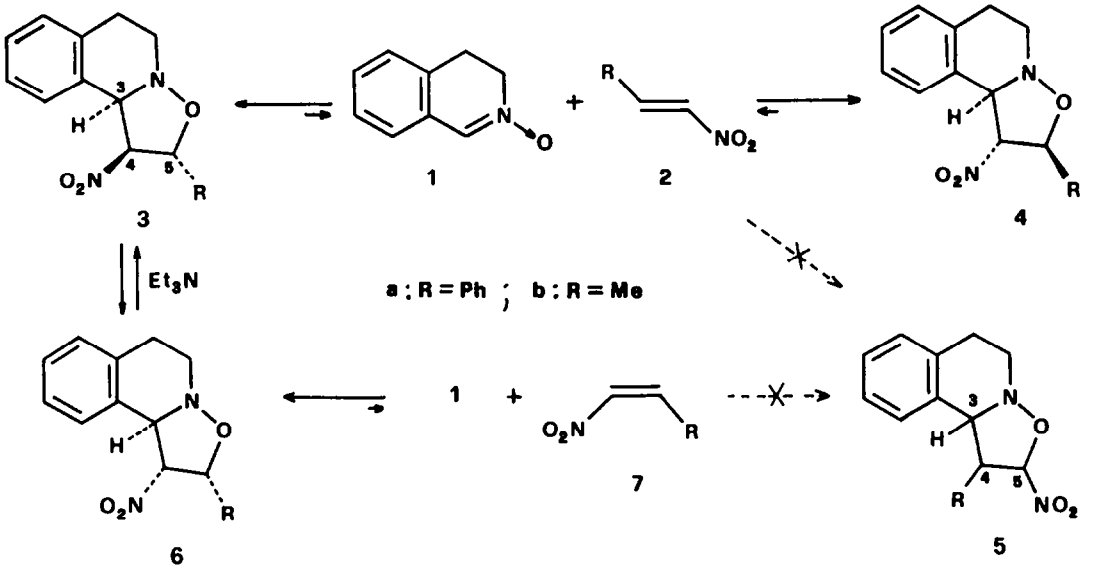
RESULTS AND DISCUSSION

We reasoned that a suitable way to attack the problem of stereoselectivity of 1,3-dipolar cycloadditions could be to study a reaction which is reversible under mild conditions. The wrong diastereoisomer, resulting from a stereochemical leakage, could accumulate in the reaction mixture over several cycloaddition-cycloreversion processes so that its final concentration could be easily detected with the usual analytical techniques. Nitrones, in particular cyclic conjugated derivatives, are 1,3-dipoles with a very high tendency to be involved in cycloreversion processes[17] and, consequently, they were obvious candidates to be used in such a study.

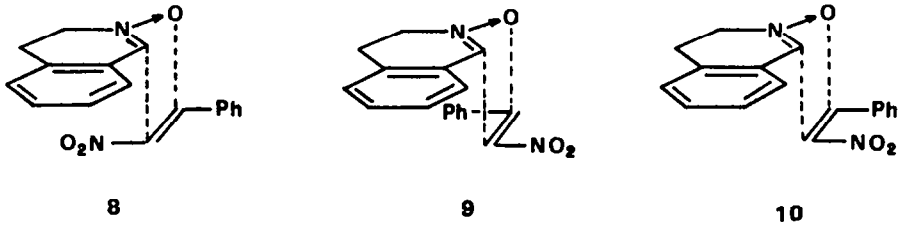
3,4-Dihydroisoquinoline-N-oxide 1 reacted readily (≃4 hrs) with excess (E)-β-nitrostyrene (2a)



Scheme 1



Scheme 2



Scheme 3

Table

^{1}HNMR (C_6D_6) and ^{13}CNMR ($CDCl_3$) spectra of adducts **3a**, **4a**, **6a** and **17a - 19a**.[a,b]

Comp.	H-3[c]	H-4[d]	H-5[e]	$J_{3,4}$	$J_{4,5}$	C-3	C-4	C-5
3a	4.80	5.15	5.95	9.0	6.0	68.1[i]	100.7	84.3
4a	5.15	4.90	5.60	3.5	6.0	67.2[i]	100.7	83.6
6a	5.55	4.92	5.32	7.0	8.5	68.0	98.5	81.4
17a[f]	3.84	5.12	5.64	7.0	6.0	67.3	96.5	78.4
18a[g]	4.23	4.45	5.35	2.0	6.0	69.9	99.2	83.2
19a[h]	4.20	4.94	5.11	1.0	7.0	68.7	98.8	82.5

[a] Numbering refers to isoxazolidine ring [b] δ in ppm and J in Hz [c] bd for **3a**, **4a** and **6a** and m for **17a-19a** [d] dd [e] d [f] δ 0.82 and 1.35 (two s, Me) [g] δ 0.82 and 1.33 (two s, Me) [h] δ 0.95 and 1.32 (two s, Me) [i] In C_6D_6

in benzene at room temperature in the dark. Monitoring the reaction mixture by ^{1}H-NMR, ^{13}C-NMR and TLC techniques showed the presence of only two products, i.e., **3a** and **4a** (Scheme 2), whose ratio changed with time. The kinetically less favoured isomer **4a**, which accounted for 15% of the initial adduct mixture, became the dominant one at the equilibrium [ratio **4a/3a** (C_6D_6) = 87:13]. The same equilibrium mixture was obtained by dissolving pure **3a** and **4a**, respectively, in C_6D_6 and no new products could be detected. Similar results were obtained by heating the reaction mixture at 53°C [kinetic ratio **3a**:**4a** ≃ 80:20 and thermodynamic ratio **4a**:**3a**=84:16 in C_6D_6] for 64 hrs.

The structure of **3a** and **4a** was assured through chemical and NMR evidence. In particular the very similar chemical shifts exhibited by the carbon atoms of the two adducts (Table) clearly indicate that they have the same regiochemistry. Likewise ^{13}CNMR data are consistent with the 5-phenyl-4-nitroisoxazolidine structures depicted in Scheme 2 for **3a** and **4a** and rule out regioisomer **5a** as a possible alternative. In fact C-4 in **5a** should resonate at a higher field than 60 ppm in contrast with the observed absorptions.

The higher $J_{3,4}$ in **3a** than in **4a** shows that the former product arises from a transition state in which the nitro group of the dipolarophile and the 1,3-dipole are endo-oriented, i.e. **8** (Scheme 3), leading to a cis H-3, H-4 relationship in the adduct. The very same $J_{4,5}$ in **3a** and **4a** supports the maintenance of the trans relationship of (E)-β-nitrostyrene.

It is worthy of note that the dominance of the endo-NO_2 adduct is not the result of stabilizing interactions between that group and the nitrone (or its phenyl ring) moiety. In fact secondary orbital interactions, electrostatic and steric effects are, as a whole, destabilizing both in **8** and **9** as clearly revealed by the preferred exo addition of **1** to nitroethylene (exo-:endo-4-nitroisoxazolidine derivative = 1.5) and to styrene (exo-:endo-5-phenylisoxazolidine derivative ≥ 18)[18]. In the case of **2a** the repulsive effect of the phenyl substituent overrides that of the nitro group by a factor of ≃ 5.7.

The higher stability of **4a** in comparison with **3a** is accounted for by higher steric crowding felt by the nitro group in **3a** than in **4a**. In fact, relief of steric compression helps to make the cycloreversion of **3a** an easy process (see below).

The isomer **6a**, absent in the cycloaddition mixtures, was obtained by treatment of compound **3a** with triethylamine in methanol whilst under the same conditions **4a** did not afford the endo-cis isomer. Base catalyzed isomerization is not a viable process for **4a** as it should lead to a sterically congested all cis-isoxazolidine, whereas a freely rotating phenyl group should accomodate a cis-relationship with a nitro group in **6a** almost as easily as does the dihydroisoquinoline residue in **3a**.

Compound **4a** was the highly dominant isomer even when all the three compounds were involved in the equilibrium [**3a**:**4a**:**6a** $\simeq$ 1:8:1; $CDCl_3$, Et_3N; **3a**$\leftrightarrows$**4a** via cycloaddition-cycloreversion processes and **3a**$\leftrightarrows$**6a** via catalyzed isomerization] while compounds **3a** and **6a** showed similar stability.

We then carried out the reaction of **2a** with excess **1** in benzene either at room temperature (1 month) or at 53°C (64 hrs) but once again **3a** and **4a** were the sole reaction products.

Control experiments showed that we could easily detect an amount of **6a** as low as 2% in the cycloaddition mixtures thus establishing a lower limit to reaction stereoselectivity as high as 98%. However the observed selectivity is not the result of a single process but the final outcome of several cycloaddition-cycloreversion reactions leading to a further significant narrowing of the possible stereochemistry loss. To put this statement on a more quantitative basis we studied the cycloreversion reactions of **3a** and **4a**.

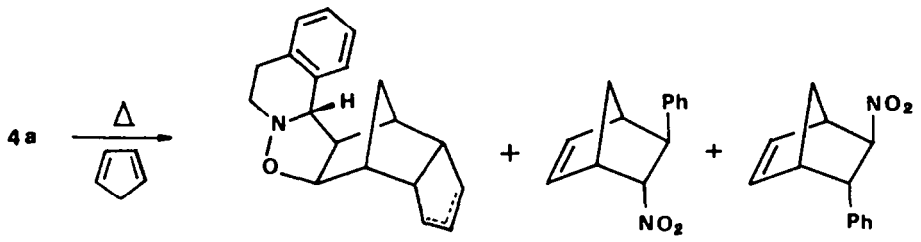
First we captured both the cycloreversion products by carrying out the reaction in cyclopentadiene as 1,3-dipole and dipolarophile trapping agent (Scheme 4). For example in the case of **4a** we isolated the adduct of **1** to the cyclopentadiene dimer, i.e., **11** and a mixture of adducts **12** and **13**. Then we followed the reactions kinetically by heating **3a** and **4a**, respectively, in the presence of N-methylmaleimide (NMM). In fact NMM reacted very quickly with **1** ($<$ 3 minutes at 33°C) to give quantitative combined yields of a 98:2 mixture of the exo adduct **14** and of the endo adduct. Compound **14** showed a surprisingly low tendency to undergo the cycloreversion reaction so that the equilibrium **1**+NMM$\leftrightarrows$**14** lay completely on the side of **14**.

The fragmentation of **3a** and **4a** obeyed first order kinetics with half-life of 0.73 hrs (k_1 = 2.65×10^{-4} sec^{-1}) and 16.2 hrs (k_1 = 1.19×10^{-5} sec^{-1}), respectively at 53°C in C_6D_6. Increased solvent polarity slightly enhanced the cycloreversion rate [**4a**:$CDCl_3$, $t_{1/2}$ = 7.1 hrs (k_1 = 2.71×10^{-5} sec^{-1}); CD_3CN, $t_{1/2}$ = 5.7 hrs (k_1 = 3.36×10^{-5} sec^{-1}).].

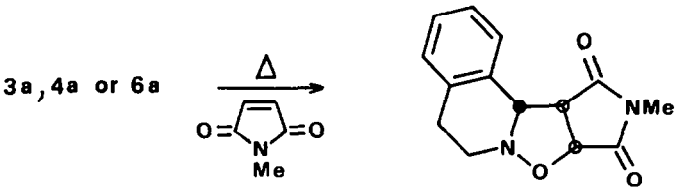
Returning to the problem of stereoselectivity of the reaction **1**+**2a**$\leftrightarrows$**3a**+**4a** it should be stressed that loss of sterochemistry has a reasonable chance to occur only in processes involving the adduct **3a** either as a final product of a cycloaddition reaction or as a starting compound of a cycloreversion reaction. In fact stereochemical leakage on the pathway from **1** + **2a** to **4a** gives rise to the all cis highly crowded and, consequently, very unstable 4-nitro-5-phenylisoxazolidine.

We can evaluate that formation of $<$2% of **6a** in a **3a**:**4a** equilibrium mixture in benzene kept at 53°C (**3a**:**4a** = 16:84) for 64 hrs implies $<$ 12.5% loss of stereochemistry for **3a**. However, during 64 hrs at 53°C every **3a** molecule is involved, in the average, in $\simeq$ 122 cycloaddition or cycloreversion processes ($2xk_1$ (**3a**) $x\,\Delta t$) leading to a retention of $>$ 99.89% ($0.875 = y^{122}$) for each individual step. Moreover at the beginning of the cycloaddition reaction at 53°C compound **3a** accounts for $\geq$ 80% of the reaction mixture and since then its percentage decreases smoothly to the equilibrium value thus making 99.89% a lowest limit for the average stereoselectivity of cycloaddition and cycloreversion reactions.[19,20]

Since our endeavours were aimed at detecting the adduct **6a**, the foregoing conclusion is based on the assumption that every "wrong" process (at least in the presence of excess **1**) must show up as



11 12 13



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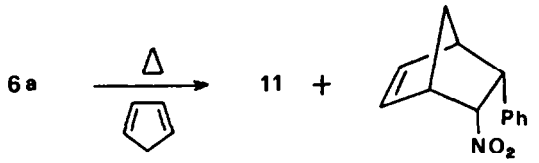

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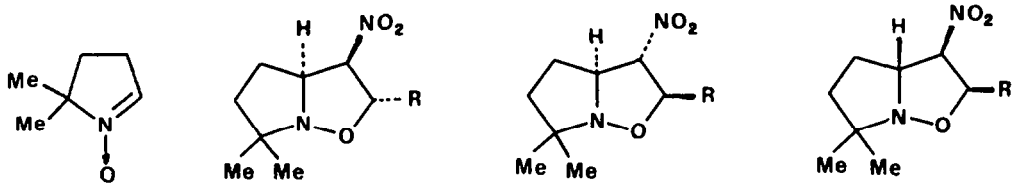
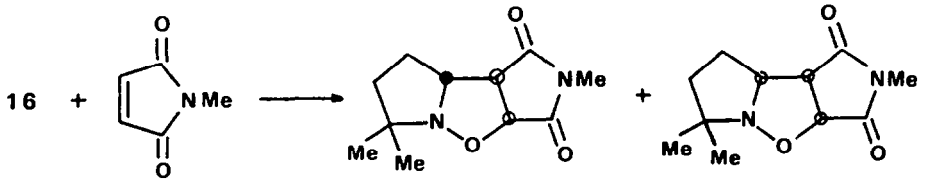
Scheme 4



16 17 18 19

a : R = Ph ; b : R = Me



20 21

Scheme 5

cis-adduct **6a** in the final mixture. However one can argue that i) nitrone acts as base inducing a ready conversion of **6a** into **3a** ii) **6a** cycloreverts more rapidly than it is formed or at least more rapidly than **3a** and **4a** iii) Z-ß-nitrostyrene (**7a**), formed in the non stereospecific fragmentation process, does not cycloadd to **1** but it is converted into the more stable (E) isomer under nitrone catalysis. In fact no examples of 1,3-dipolar cycloadditions to (Z)-ß-nitrostyrene have so far been reported. Moreover Huisgen has recently shown that azomethine imines do catalyze the conversion (Z)→(E)-ß-nitro styrene without giving any adduct to the cis-dipolarophile.[12]

We addressed these three issues and found that i) **6a** was not appreciably converted into **3a** (or mixture **3a**, **4a**) in the presence of **1** under the above reported cycloaddition conditions ii) adduct **6a** did cyclorevert (Scheme 4) but its fragmentation was slower [$t_{1/2}$ = 7.0 hrs (k_1 = 2.75x10^{-5} sec^{-1}) at 80°C in $CDCl_3$] than that of **3a** and **4a**[21] iii) (Z)-ß-nitrostyrene (**7a**) reacted easily with **1** and competition reactions of **1** with excess 1:1 mixtures of nitrostyrene isomers showed that the reaction rate of the (Z)-isomer is definitively higher than that of the (E)-isomer.

Although this is the first exception to the rule that "cis-disubstituted ethylenes are less reactive dipolarophiles than the related trans-isomers"[22] it does not completely come as a surprise. In fact it is well known that nitrones follow this rule somewhat reluctantly as shown by the 2.9 ratio found for the reactions of N-methyl-C-phenyl nitrone with fumaric and maleic esters.[22] Moreover, as stated above, the interactions of the nitrone with the nitro group in **8** and with the phenyl group in **9** are repulsive whilst nitrone **1** can avoid both of them in the exo-transition state **10** (Scheme 3) from the cis dipolarophile. These superimposed secondary effects do not leave room for a precise conclusion about the relative intrinsic propensity of the double bonds of **2a** and **7a** to enter 1,3-dipolar cycloaddition with nitrones.

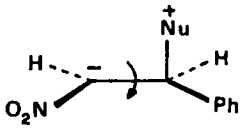
What about going significantly beyond 99.89% in order to get closer to a figure of 100%?

The possibility of side reactions (base catalyzed cis ⇄ trans interconversion of nitrostyrenes[12] and of **3a**⇄**6a**) makes such an endeavour meaningless. For example TLC analysis of a solution of **4a** in C_6D_6, left equilibrating for six months at 24°C in a NMR tube, showed the presence of trace amounts of **6a** along with the equilibrium mixture **4a** + **3a**⇄**1** + **2a**. In our opinion this result, rather then questioning the concertedness of the reaction, warns one about the possibility of stereochemical loss in the educts and/or in the adducts under reaction and/or work up conditions. Moreover erratic amounts (<3%) of adduct **6a** were isolated upon chromatography on silicagel of the reaction mixtures.[13,15]

We then examined the reaction of 5,5-dimethylpyrroline-N-oxide (**16**) with (E)-ß-nitrostyrene which resulted regio and endo-NO_2 specific with formation of the sole trans-adduct **17a** (Scheme 5). Compound **17a** was converted into **18a** upon heating in the presence of **2a** (equilibrium ratio **18a**:**17a** 88:12) whilst on treatment with triethylamine it isomerized smoothly to **19a** (equilibrium ratio **17a**:**19a** ≃1:1 in $CDCl_3$). In the cycloreversion studies of **17a** [$t_{1/2}$ = 1.35 hrs (k_1 = 1.43x10^{-4} sec^{-1}) at 80°C in $CDCl_3$] the 1,3-dipole **16** was trapped with NMM to give a mixture of exo **20** and endo **21** adducts (exo:endo = 86:14) (Scheme 5). The reaction of **16** with excess 1:1 mixtures of (E) and (Z)-ß-nitrostyrene confirmed the (Z)isomer as more reactive (at least ten times) than the (E) derivative towards cyclic nitrones. Also worthy of note is the finding that the reaction of **16** with the pure (Z) isomer is accompanied by slower (Z)→(E) isomerisation.

Base or 1,3-dipole catalyzed (Z)→(E) conversion calls for an intermediate of the type **22**[12] thus suggesting that the intermediacy of **23** and **24** on the pathway from educts to adducts would have led to an extensive or at least easily detectable loss of stereochemistry. Dipolar intermediates

are also ruled out by the low solvent polarity effect on the reaction rates of **16** with **2a** (a small retarding effect parallels increased solvent polarity) and with **7a** (practically no effect).



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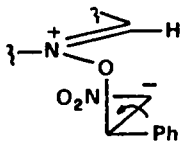

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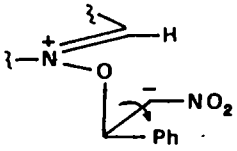

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Finally 1-nitro-1-propene (**2b**) reacted with **1** and **16**, respectively, to give adducts with the same regioselectivity and similar endo-exo selectivity to that reported above for **2a**. The adduct **3b** (Scheme 2) cycloreverted at room temperature ($t_{1/2}$ = 9.5 hrs at 33°C in $CDCl_3$) whereas **17b** (Scheme 5) required prolonged heating in toluene at reflux. The relative fragmentation rates **3a**> **3b**, **3a**> **17a** and **17a**> **17b** are clear manifestation of the "conjugation gain" on going from adducts to educts proposed as one of the dominant elements which promote 1,3-dipolar cycloreversion[17].

CONCLUSION

We have found compelling evidence that cyclic nitrone cycloadditions with (E)-and (Z)-ß-nitrostyrene can reasonably be classified as stereospecific. Eventual loss of stereochemistry should be ascribed to a trivial base (or acid) catalyzed cis-trans isomerization in the adducts and/or in the educts. A concerted cycloaddition fits well the foregoing experimental data.

The higher reactivity of cyclic nitrones with (Z)-ß-nitrostyrene than with (E)-ß-nitrostyrene represents the first example, as far as we know, of a cis 1,2-disubstituted olefin reacting faster than the related trans compound in 1,3-dipolar cycloadditions. Secondary repulsive interactions present in either one of the transition states from the trans-dipolarophile but not in the exo transition state from the cis olefin are advanced as an important factor which could lower the reactivity of the trans-olefin.

Finally we have observed that isoxazolidines deriving from cis-dipolarophiles exhibit a lower tendency to enter 1,3-dipolar cycloreversion than isoxazolidines formed from trans-olefins. This finding led us to undertake further systematic research aimed at finding out whether or not the rule "Trans olefins are formed faster than related cis olefins in 1,3-dipolar cycloreversions" holds.

EXPERIMENTAL

Melting points are uncorrected. Elemental analyses were made on a Carlo Erba CHN analyzer mod. 1106. ^1H and ^{13}CNMR Spectra were recorded on a Bruker WP80SY Spectrometer (operating at 80 and 20.2 MHz) equipped with an Aspect 2000 computer with tetramethylsylane as internal standard. Thin layer chromatography was carried out on plates precoated with Silicagel 60 GF_{254} Merck. Spots were revealed either by spraying with 3% chromic oxide in sulphuric acid (50%) followed by heating at 120°C or under UV light (254 nm). Column chromatography was performed with Silicagel 60 (70-230 mesh) Merck eluting with cyclohexane-ethyl acetate mixtures. $CDCl_3$ was dried over K_2CO_3 and distilled before use. Commercial (E)-ß-nitrostyrene was crystallyzed twice from EtOH. (Z)-ß-nitrostyrene was obtained by irradiating the (E) isomer in benzene (Pyrex filter, high pressure mercury lamp).[23] The resulting reaction mixture was subjected to fast column chromatography eluting with benzene to give a ≃ 3:1 mixture of (Z) and (E) isomers. In one instance we succeded in isolating small amounts of the (Z)-isomer free from the (E) derivative.

(E)-1-Nitro-propene was prepared by dehydration of 1-nitro-2-propanol[24] with phthalic anhydride. ^1H-NMR analysis of the product showed the presence of ≃ 8% of (Z)-1-nitro-1-propene. All the cycloaddition and cycloreversion reactions involving **2a** and **7a**, respectively, were carried out in the dark.

Reaction of 3,4-dihydroisoquinoline-N-oxide (1) with (E)-β-nitrostyrene (2a). Compound **2a** (60 mg, 0.40 mmol) and freshly distilled nitrone **1** (44 mg, 0.30 mmol) were dissolved in C_6D_6 (0.5 ml) and the reaction monitored by ^{1}H-NMR, ^{13}C-NMR and TLC techniques. After 4 hrs at 24°C **1** had almost completely disappeared and only compounds **3a** and **4a** (85:15) were detected in the reaction mixture. The reaction was kept at 24°C for a month and after that time a 13:87 ratio of **3a**:**4a** could be evaluated from the ^{1}H-NMR spectrum but no new products could be detected by the foregoing techniques.

Similar results were obtained by carrying out the reaction in $CDCl_3$ (kinetic ratio, **3a**:**4a** = 86:14; thermodynamic ratio, **3a**:**4a** = 15:85). The chemical shifts of protons of **3a** and **4a** in $CDCl_3$ were as follows: **3a**, δ 5.22 (d, H-3, J3,4 = 9.0 Hz), 5.58 (dd, H-4, J 4,5 = 6.0 Hz), 6.02 (d, H-5); **4a**, δ 5.16 (dd, H-4, J3,4 = 3.5 Hz and J4,5 = 6.0 Hz), 5.38 (d, H-3), 5.62 (d, H-5). Heating the reaction mixtures for several hours (53 and 64 hrs, respectively, for $CDCl_3$ and C_6D_6 solutions) did not make **6a** appear as a clearly detectable spot upon TLC analysis. By contrast the spot of **6a** was clearly visible when 1.8 mg of **6a** were added to the above described reaction mixtures.
Pure **3a** and **4a**, respectively, dissolved in C_6D_6 and kept at 24°C for a month gave rise to a 13:87 mixture of **3a** and **4a** in equilibrium with the starting compounds **1** and **2a** (Adducts:Educts > 10:1). After further five months in the NMR tube at this temperature, TLC analysis disclosed the presence of trace amounts of **6a**.

Compound **6a** was not detected when the reaction of excess **1** (60 mg, 0.41 mmol) with **2a** (45 mg, 0.30 mmol) was carried out either in C_6D_6 or $CDCl_3$ (Two sets of experiments:at 24°C for a month in both solvents and at 53°C for 64 hrs in C_6D_6 and for 56 hrs in $CDCl_3$). Longer heating (e.g. 125 hrs at 53°C) led to appearance of trace amounts of **6a** (< 2%) but detection was made less reliable by the presence of small amounts of decomposition products.

The adducts **3a** [colourless needles, m.p. 86-87°C (Found: C,69.2; H,5.5; N,9.5. Calc. for $C_{17}H_{16}N_2O_3$; C,68.9; H,5.4; N,9.5;)] and **4a** [colourless platelets from cyclohexane, m.p. 97-99°C (Found:C, 69.1; H,5.3; N,9.6.)] were isolated by column chromatography. In some instances column chromatography of the reaction mixture led to isolation of small amounts (< 3%) of **6a**. Compounds **4a**, **3a** and **6a** were eluted (cyclohexane:ethyl acetate = 85:15) in the order.

Synthesis of 6a. Equimolar amounts of **1** (300 mg) and **2a** (305 mg) were reacted in benzene (2 ml) at room temperature. After 5 hrs the solvent was carefully evaporated under reduced pressure , the crude residue dissolved in methanol and to the resulting solution was added triethylamine (0.5 ml). Seeding with crystals of **6a** brought about the precipitation of pure **6a**. After further 5 hrs the precipitate was filtered off (250 mg, 41%) and purified as colourless needles from benzene, m.p. 160-1° dec. (Found: C,68.9; H,5.5; N,9.5). [H-3, H-4 and H-5 resonate as complex multiplets at δ 5.40 -5.95 in $CDCl_3$].

Compound **6a** could also be prepared by reacting **1** with excess **2a**/**7a** mixture (**2a**:**7a** = 1:3) in benzene. Due to the higher reactivity of **7a** than of **2a** the feebly soluble **6a** precipitated in a pure state from the reaction mixture (≥ 75%).

Cycloreversion Reactions. A solution of **4a** (50 mg) in freshly distilled cyclopentadiene (1.5 ml) in the presence of small amount of hydroquinone was heated in a sealed ampoule at 70°C for 15 hrs. Column chromatography of the crude product furnished a mixture of **12** and **13** (28 mg, **12**:**13** 4.5),[25] E-β-nitrostyrene (6 mg), **4a** (3 mg) and **11** [43 mg; colourless needles from petrol ether, m.p. 113-117°C (Found C, 81.9; H, 7.4; N, 5.3; Calc. for $C_{19}H_{21}NO$:C, 81.7; H, 7.6; N, 5.0.)].

Under similar conditions compound **6a** (50 mg in 1,5 ml of cyclopentadiene and 0.5 ml of methylene chloride in a sealed ampoule at 70°C for 15h) gave rise to **15** [7 mg, yellow oil, δ ($CDCl_3$) 1.75 (m, 2H), 3.15 (m, 1H), 3.50 (m, 1H), 3.93 (dd, 1H, J =3.0 and 10.0 Hz), 5.47 (dd, 1H, J = 3.2 and 10.0 Hz), 6.42 (dd, 1H, J = 3.0 and 6.9 Hz), 6.62 (dd, 1H, J = 3.0 and 6.0 Hz)] and **11** (12 mg) in addition to recovered starting product (36 mg).

Authentic samples of **11**, **12**, **13** and **15** were obtained from the reaction of **1**, (E)- and (Z)-β-nitrostyrene, respectively, with cyclopentadiene.
Kinetic runs were carried out by dissolving 30 mg (0.1 mmol) of the adducts and 23 mg (0.2 mmol) of N-methylmaleimide in 0.5 ml of the appropriate solvent . The concentrations of the adducts **3a**, **3b**, **4a**, **6a** and **17a**, respectively, were obtained by integrations of H-3, H-4 and H-5 signals whilst those of **14** and **20** by integrations of H-3 and H-5 signals. During heating under the conditions employed for rate analyses no significant side reactions took place. The first order rate constants for the cycloreversion were obtained by least-squares treatment of ln a/(a-x) (a is the initial concentration of the adduct which undergoes cycloreversion) vs t. Fragmentations of **3a** and **3b** at 33°C were carried out in the NMR probe whereas in the other cases sealed NMR tubes were heated in a thermostat (± 0.1°C) and spectra recorded at appropriate time intervals (at least seven spectra over two half-lives). **3a** ($CDCl_3$, 33°C, two runs):$k_1 = 8.55 \pm 0.33 \times 10^{-5}$ sec^{-1}. **3a** (C_6D_6, 53°C, two runs):$k_1 = 26.5 \pm 0.3 \times 10^{-5}$ sec^{-1}. **4a** ($CDCl_3$, 53°C, three runs):$k_1 = 2.71 \pm 0.03 \times 10^{-5}$ sec^{-1}. **4a** (CD_3CN, 53°C, two runs):$k_1 = 3.36 \pm 0.08 \times 10^{-5}$ sec^{-1}. **4a** (C_6D_6, 53°C, two runs):$k_1 = 1.19 \pm 0.03 \times 10^{-5}$ sec^{-1}. **6a** ($CDCl_3$, 80°C, two runs):$k_1 = 2.75 \pm 0.06 \times 10^{-5}$ sec^{-1}. **3b** ($CDCl_3$, 33°C, two runs):k_1 =

$2.02 \pm 0.1 \times 10^{-5}$ sec^{-1}. **17a** ($CDCl_3$, 80°C, two runs): $k_1 = 14.3 \pm 0.1 \times 10^{-5}$ sec^{-1}.

Base catalyzed isomerization of **3a, 4a, 6a, 17a** and **18a**. Compounds **4a** and **18a** (50 mg), respectively, were dissolved in $CDCl_3$ (0.5 ml) in the presence of triethylamine (3 mg) and kept at room temperature for 65 hrs. After that time only the signals of the starting product (and triethylamine) were present in the ^{1}HNMR spectrum of the reaction mixture in the case of **18a**, whereas in the case of **4a** minor amounts of **1** and **2a** and trace amounts of **3a** were detected by TLC and ^{1}HNMR analysis of the reaction mixture.

^{1}HNMR analysis showed that the equilibration of compound **17a** under similar conditions led to a 1:1 mixture of **17a** and **19a** which were separated by column chromatography.

In the case of **3a** [50 mg in $CDCl_3$ in the presence of triethylamine (3 mg)] base catalyzed isomerization and cycloreversion-cycloaddition processes competed with each other giving rise to a mixture of **1**, **2a**, **3a**, **4a** and **6a** (**3a**:**4a**:**6a** ≃ 1:8:1 at the equilibrium).
The same equilibrium mixture was obtained from **6a** under similar conditions. By contrast, the ^{1}H-NMR spectrum of a solution of **6a** (24 mg) and **1** (9 mg) in $CDCl_3$ (0.5 ml) did not show any significant change on heating at 53°C for 100 hrs.

Reaction of **1** and **16** with N-methylmaleimide. A NMR tube containing a solution of **1** (18 mg, 0.12 mmol) and NMM (22 mg, 0.20 mmol) in C_6D_6 was placed in the NMR probe (at 33°C) and the reaction monitored at time intervals of 30 seconds. After 3 minutes the signals of **1** had completely disappeared. Then the reaction was carried out on a larger scale [237 mg of **1** and 180 mg of NMM in benzene (3 ml)] at r.t. The precipitated crystalline **14** (360 mg) was filtered off and mother liquors column chromatographed to give a further crop of **14** [49 mg (Total yield:98%) colourless prisms from MeOH, m.p. 164-166°C. δ(C_6D_6), 2.67(s, NMe), 4.22 (d, H-5, J4,5 = 7.0 Hz), 4.60 (bs, H-3); δ ($CDCl_3$) 3.05 (s, NMe) 3.75 (dd, H-4, J4,5 = 7.0 Hz and J3,4 = 2.0 Hz), 4.83 (bs, H-3), 4.83 (d, H-5); δ (CD_3CN), 3.00 (s,NMe), 3.78 (dd, H-4, J4,5 = 7.0 Hz and J3,4 = 3.0 Hz), 4.72 (bs H-3), 4.88 (d, H-5). (Found C, 64.9; H, 5.7; N, 10.7. Calc. for $C_{14}H_{14}N_2O_3$:C, 65.1; H, 5.5; N, 10.85.)] and the endo adduct [7 mg (2%); m.p. 100-102°C. δ (C_6D_6), 2.40 (s, NMe), 2.97 (t, H-4, J3,4 = 7.0 Hz and J4,5 = 7.0 Hz), 3.73 (broad signal, H-3), 4.23 (d, H-5); δ ($CDCl_3$), 2.90 (s, NMe), 3.98 (t, H-4, J3,4 = 7.0 and J4,5 = 7.0 Hz), 4.30 (broad signal, H-3), 4.97 (d, H-5)]. The endo adduct was transformed into the exo **14** upon heating.
The reaction of **16** (113 mg, 1.0 mmol) with NMM (133 mg, 1.2 mmol) in C_6H_6 (2 ml) at r.t. for 1 hr led to a mixture of **20** [185 mg (82%), colourless needles from cyclohexane, m.p. 132-133°C. δ ($CDCl_3$) 1.02 and 1.35 (two s, Me), 3.02 (s, NMe), 3.49 (d, H-4, J4,5 = 7.5 Hz), 3.96 (m, H-3), 4.79 (d, H-5). (Found: C, 58.6, H, 7.4; N, 12,3. Calc. for $C_{11}H_{16}N_2O_3$:C, 58.9; H, 7.2; N, 12.5)] and **21** [30 mg (13%), colourless needles, m.p. 120-122°C. δ (C_6D_6) 0.75 and 1.30 (two s, Me), 2.55 (s, NMe), 3.10 (dd, H-4, J3,4 = 8.0 Hz, J4,5 = 7.5 Hz), 3.55 (m, H-3), 4.22 (d, H-5). (Found, C, 59.2; H, 7.0; N, 12.6.)].

Reaction of **16** with **2a**. A solution of **2a** (40 mg, 0.27 mmol) and **16** (20 mg, 0.18 mmol) in C_6D_6 (0.5 ml) was kept at 33°C. After 9 hrs (50% conversion on the basis of reacted **16**) the ^{1}HNMR of the reaction mixture displayed only the signals of **17a** while after 18 hrs very weak signals of **18a** appeared in the spectrum and TLC analysis showed the presence of small amounts of **19a**. On a preparative scale the reaction was conducted with 300 mg of **2a** and 150 mg of **16** in C_6H_6 (5 ml) at 24°C for seven days. Then the solution was chromatographed to give **17a** [250 mg (72%), slight yellow prisms from petrol ether, m.p. 49-52°C (Found C, 64.5; H, 6.7; N, 10.6. Calc for $C_{14}H_{18}N_2O_3$: C, 64.1; H, 6.9; N, 10.7.)] and **19a** [36 mg (10%), colourless prisms from cyclohexane, m.p. 134-137°C (Found C, 64.2; H, 6.9; N, 10.7.)] The presence of **19a** in the reaction mixture at the end of the reaction (but not at the beginning) can, in our opinion confidently be ascribed to base catalyzed isomerization of **17a** due to the higher basic strength of **16** as compared with **1**. In fact the cycloreversion reaction of **17a** is very slow at room temperature so that the presence of **19a** cannot be the consequence of a loss of stereochemistry over several cycloaddition-cycloreversion processes. Further interconversion **17a** → **19a** was brought about by Silicagel catalysis during column chromatography. Isomerization **17a** → **19a** took place also when pure solid **17a** was kept at room temperature for several months.

The above reaction, repeated in CD_3CN, under otherwise similar conditions, reached 50% conversion after 24 hrs.

In a further experiment a solution of **2a** (200 mg) and **16** (100 mg) in C_6H_6 was heated under reflux for 72 hrs. Evaporation of the solvent followed by column chromatography furnished a mixture of **17a** and **18a** [180 mg (78%), **18a**:**17a**=94:6; **18a** was purified by crystallization from petrol ether as colourless prisms m.p. 61-63°C. (Found: C, 63.8; N, 6.7; N, 10.8.)] and **19a** (21 mg, 9%).

Reaction of **16** with (Z)-β-nitrostyrene (**7a**). The reaction of **16** (20 mg) with **7a** (50 mg of a 3:1 mixture of **7a** and **2a**) at 33°C reached 50% conversion after ≃ 1 hr both in C_6D_6 and CD_3CN and ^{1}HNMR and TLC analyses clearly showed that **2a** did not compete efficiently with **7a**. After 24 hrs compound **19a** (42 mg, 90%) was isolated by column chromatography.
In a further experiment pure (^{1}HNMR) **7a** (10 mg) was reacted with excess **16** (15 mg) in $CDCl_3$. After two hrs the ^{1}H-NMR spectrum clearly exhibited the signals of **2a** aside from those of **7a** and **19a**.

Competition reactions of **1** and **16** with mixtures **2a**/**7a**. A solution of **1** (100 mg) and excess 1:1

mixture of **2a** and **7a** (600 mg) in benzene (5 ml) was kept at 21°C for two hrs. Then fast column chromatography allowed isolation of **6a** (155 mg) and of **3a+4a** (10 mg). TLC analysis clearly showed that compound **6a** was highly dominant already at the very beginning of the reaction. These data are clear evidence of higher reactivity of **7a** than **2a** even if possible partial conversion of **7a** into **2a** as well as loss of compound **3a** (due to its high propensity to cycloreversion) do not allow a precise evaluation of the cycloaddition rate ratio between **2a** and **7a**.

Likewise **16** (100 mg) was reacted with excess **2a/7a** (1:1) mixture (1.03 g) in benzene (5 ml, 21°C, 8 hrs). Once again TLC analysis showed clearly that **7a** reacted faster than **2a** and column chromatography furnished **19a** (155 mg) and **17a** (15 mg).

Reaction of **1** and **16** with 1-nitro-1-propene. The reaction of **1** with excess 1-nitropropene (containing ≃ 8% of the cis isomer) in C_6D_6 at 21°C gave rise to a kinetic mixture of **3b** and **4b** [^{13}C-NMR (after two hrs): **3b**:**4b** ≃ 4:1; **3b**, δ (C_6D_6) 17.7 (q), 29.1 (t), 47.8 (t), 68.0(d), 78.9 (d), 99.9 (d); **4b**, δ (C_6D_6) 13.2 (q), 23.1 (t), 49.2 (t), 66.6 (d), 77.9 (d), 100.2 (d).] while at 80°C (24 hrs) adduct **4b** was highly dominant (90%). Compound **6b** was also present in minor amounts in the reaction mixtures.

3b: slightly yellow needles from petrol ether, m.p. 117-118°C; δ ($CDCl_3$) 1.57 (d, Me, JMe,H-5 = 6.0 Hz), 5.00-5.50 (m, 3H, H-3, H-4 and H-5). (Found: C, 61.7; H, 6.2; N, 11.8 Calc. for $C_{12}H_{14}N_2O_3$: C, 61.5; H, 6.0; N, 12.0.).

4b: colourless platelets from petrol ether, m.p. 68-69°C; δ ($CDCl_3$) 1.41 (d, Me, JMe,H-5 = 6.0 Hz), 4.40-4.85 (m, H-4 and H-5), 5.32 (bd, H-3, J3,4 = 3.0 Hz). (Found:C, 61.3; H, 5.9; N, 12.1.).

6b: slightly yellow needles from petrol ether, m.p. 115-116°C; δ (C_6D_6) 1.10 (d, Me, JMe,H-5 = 6.0 Hz), 4.39 (m, H-5, J4,5 = 8.0 Hz), 4.71 (dd, H-4, J3,4 = 7.0 Hz), 5.36 (bd, H-3). (Found:C, 61.6; H, 6.0; N, 12.3.).

Nitrone **16** (113 mg, 1.0 mmol) reacted with excess nitropropene (200 mg, 2.3 mmol) in C_6H_6 at r.t. to give **18b** [12 mg (6%), colourless prisms from petrol ether, m.p. 72-74°C. δ (C_6D_6) 0.77 and 1.30 (two s, Me), 1.03 (d, Me, J,Me,H-5 = 6.0 Hz), 3.90 (dd, H-4, J3,4 = 2.0 Hz and J4,5 = 6.0 Hz), 4.14 (m, H-3) and 4.26 (m, H-5). (Found: C, 53.7; H, 8.3; N, 14.2. Calc. for $C_9H_{16}N_2O_3$:C, 54,0; H, 8.1; N, 14.0.)] and **17b** [174 mg (87%), colourless oil. δ ($CDCl_3$) 1.07 and 1.37 (two s, Me), 1.41 (d, Me, JMe,H-5 = 6.0 Hz), 4.32 (m, H-3), 4.67 (m, H-5, J4,5 = 8.0 Hz), 5.12 (dd, H-4, J3.4 = 7.8 Hz). (Found: C, 53.8; H, 8.0; N, 14.3.)] which was contaminated by **19b**. On standing at r.t. compound **17b** was completely converted into **19b** [colourless prisms from petrol ether, m.p. 82-85°C. δ($CDCl_3$) 1.15 and 1.35 (two s, Me), 1.29 (d, Me, JMe,H-5 = 6.0 Hz), 4.52 (m, 2H, H-3 and H-5), 5.10 (dd, H-4, J 3,4=0.5 Hz and J 4,5=6.0 Hz). (Found: C, 54.2; N, 8.2; N, 13.9.)].

A solution of **17b** (150 mg) and **2b** (100 mg) in toluene (5 ml) was heated at reflux for 30 hrs. Usual work up led to isolation of **18b** (65 mg) and **19b** (20 mg).

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